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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,797	02/11/2004	Gregory Grabowski		4885

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,797	GRABOWSKI ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-63* is/are pending in the application.

4a) Of the above claim(s) *37-50, 62, and 63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner prosecuting this case has changed. All inquiries directed to the application should be directed to examiner W. - C. Winston Shen.

This application 10/776,797 filed on 02/11/2004 is a DIV of 09/775,517 02/02/2001 PAT 6,849,257 which claims benefit of 60/180,362 02/04/2000.

Specification

It is noted that the applicants filed preliminary amendment in specification on 2/11/2004 as follows: "This application is a divisional of U.S. Patent Application Serial No. 09/775,517, filed on February 2, 2001, which is based on and claims priority from U.S. Provisional Patent Application Serial No. 60/180,362, Gregory A. Grabowski and Hong Du, filed February 4, 2000". The status of parent application referred to in the preliminary amendment needs to be updated.

Election/Restriction

1. Applicant's election with traverse of Group II, Claims 51-61, drawn to a method of providing biologically active lipid hydrolyzing protein or polypeptide or mixtures thereof, to cells of a mammal having deficiency in biologically active lipid hydrolyzing protein or polypeptide, said method comprising administration into cells a vector comprising and expressing a DNA sequence encoding biologically active lipid hydrolyzing protein or polypeptide, in the reply filed on Jan. 19, 2007 is acknowledged. The traversal is on the ground(s) that (i) the Examiner has not made a Prima Facie Showing that Combining the Claims

of Group II and Group III would Impose a "Serious Burden" as Required by MPEP § 803, (ii) Combining Groups II and III would not impose a "Serious Burden" on the Examiner as Required by MPEP § 803, and (iii) all of these claims relate to a method of providing a biologically active lipid hydrolyzing protein or polypeptide to cells of a mammal comprising administering into cells a vector comprising a DNA sequence encoding the biologically active protein. The traversal is not found persuasive because, as indicated in the Restriction Requirement, different and distinct steps and modes of operation are required for treating different diseases or deficiencies in a mammal. Group II is directed to the limitation of a mammal having deficiency in biologically active lipid hydrolyzing protein whereas Group III is to treat atherosclerosis in a mammal. The mammals encompassed by of Group II and III are patentably distinct because atherosclerosis is not necessarily associated with deficiency in biologically active lipid hydrolyzing protein.

With regard to the elected Group II, the Examiner notes that the limitation "lipid hydrolyzing protein" recited in claim 51 is a genus whereas the limitation "lysosomal acid lipase" recited in claim 56 is a species of the genus "lipid hydrolyzing protein".

Therefore, claims 37-50 and 62-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicants cancelled the claims 1-36.

The requirement is still deemed proper and is therefore made FINAL.

Status of claims: claims 51-61 are currently under examination.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 54 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is noted that there is no polypeptide sequence of any lysosomal acid lipase disclosed in the specification.

The phrase "substitution of amino acid Pro(-6) to Thr and Gly2 to Arg" recited in claim 55 of instant application is vague and indefinite. Does Gly2 indicate the second amino acid of the recited lysosomal acid lipase being an amino acid residue glycine? It is also unclear what "(-6)" means in the term "Pro(-6)".

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 51-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is noted that the term "lipid hydrolyzing protein" recited in claim 51 is considered as a broad genus, which encompass "lysosomal acid lipase" as a species. Nevertheless, the term "lysosomal acid lipase" recited in claim 56 is also considered as a genus, which encompasses species comprising variants, and fragments thereof any "lysosomal acid lipase". It is noted that there is variability of proteins within the broader genus "lipid hydrolyzing protein", which reads on all lipolytic enzymes during lypolysis, including lipases. There is no evidence that the asserted lipid hydrolyzing protein cDNA had a known structural relationship to any other lipid hydrolyzing protein cDNA sequences.

The claims are directed a method of producing a biologically active polypeptide in a mammal, an isolated nucleic acid molecule, a vector comprising the same nucleic acid molecule, mammalian host cells comprising the same nucleic acid molecule, and pharmaceutical compositions comprising the same nucleic acid molecule.

With regard to claims 56-61, the nucleotide sequences that encode lysosomal acid lipases, variants, and fragments thereof encompassed within the genus of nucleotide molecules have not been disclosed. Based upon the prior art there is expected to be variation among the species of DNA, which encode lysosomal acid lipases, because the sequence of lysosomal acid lipase DNAs would be expected to vary among individuals. The specification does not disclose any nucleotide sequence that encodes a lysosomal acid lipase from mammalian lipase DNAs or human lipase DNAs or other lysosomal acid lipase DNAs from other cell types. There is no evidence on the record of a relationship between the structure of any lysosomal acid lipase cDNA and the claimed lysosomal acid lipase DNA that would provide any reliable information about the structure of other lysosomal acid lipase DNAs within the genus. There is no evidence

on the record that the asserted lysosomal acid lipase DNA had a known structural relationship to any other lysosomal acid lipase cDNA sequences; the specification discloses none of lysosomal acid lipase DNA obtained from any origin; the art indicated that there is variation between lysosomal acid lipase lipase DNA sequences and their functions. The specification has not even disclosed the type (or splicing variant) of lysosomal acid lipase that the claimed DNA encodes. In the absence of a functional assay it would not be possible to test variants of the claimed sequences for biological activity. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because no lysosomal acid lipase DNA sequence is presented as a representative of the claimed genus. Consequently, since Applicant was not documented in possession of any lysosomal acid lipase DNA and since the art recognized variation among the species of the genus of DNAs that encode lysosomal acid lipases, the claimed lysosomal acid lipase DNA was not considered as a representative of the claimed genus. Therefore, Applicant was not in possession of the genus of lysosomal acid lipase cDNAs as encompassed by the claims. Accordingly, Applicant was not in possession of the even broader genus of "lipid hydrolyzing protein" DNAs as encompassed by the claims 51-55. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

In addition to the abovementioned issues in written description, the phrase "at least 85% sequence homology to lysosomal acid lipase" recited in claim 54 of instant application was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the absence of any polypeptide sequences of any lysosomal acid lipase disclosed in the specification, what would be the basis for determination of the phrase "at least 85% sequence homology"? Moreover, based on the information disclosed in the specification of instant application, a lysosomal acid lipase (LAL), a member of the lipase family, is a 372 amino acid glycoprotein (See lines 1-2, paragraph [0037], instant application), 15% of 372 amino acids would account for more than 55 amino acids. Each amino acid could be altered to one of the other 19 amino acid residues (when only L-form standard amino acid residues is considered); accordingly, there would be 19^{55} different variations, which is equivalent to 2.1×10^{70} different patentably distinct polypeptides.

4. Claims 51-61 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

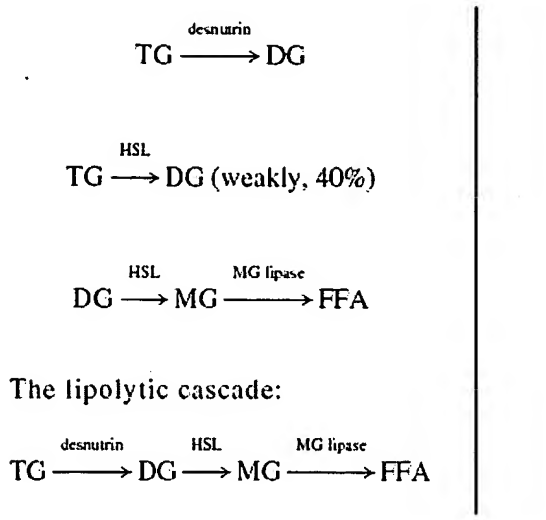
Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The nature of the invention: The nature of the invention is directed to a method of gene therapy comprising administration of a vector comprising a polynucleotide sequence encoding a lipid hydrolyzing protein to a mammal having a deficiency in the said lipid hydrolyzing protein.

The breadth of the claims: The breadth of the invention encompasses any method for providing any biologically active lipid hydrolytic protein to any cells of any mammal having deficiency in any biologically active lipid hydrolytic protein, said method comprising any route of administration into cells any vector comprising and expressing any DNA sequence encoding any biologically active lipid hydrolytic protein and expressing the DNA sequence in said cells to produce the said biologically active lipid hydrolytic protein.

The state of the prior art: Wolf summarized the molecular mechanism of mobilization of fat from adipose tissue as follows (where TG, triglycerides; DG, diglycerides; MG, monoglycerides) (See abstract, Wolf, The mechanism and regulation of fat mobilization from adipose tissue: desnutrin, a newly discovered lipolytic enzyme. *Nutr Rev.* 63(5): 166-70, 2005).



With regard to gene therapy for lysosomal acid lipase deficiency, Du et al. teach that lysosomal acid lipase (LAL) is the essential enzyme for hydrolysis of triglycerides (TGs) and cholesteryl esters (CEs) in lysosomes. Its deficiency produces two human phenotypes: Wolman disease (WD) and cholesteryl ester storage disease (CESD). The LAL null (lal(-/-)) mouse mimicks aspects of human WD and CESD. The potential for gene therapy of LAL deficiency was tested with first-generation adenoviral vectors containing human LAL cDNA (Ad-hLAL) by intravenous injection into lal(-/-) mice. Compared with phosphate-buffered saline-injected controls, the mice receiving Ad-hLAL had increased hepatic LAL activity, decreased hepatomegaly, and normalization of histopathology. The studies by Du et al. provided the basis for the use of gene therapy, in the form of gene transfer via intravenously administered adenovirus, to correct deficiency states, such as WD and CESD, and histopathology of a variety of tissues (See abstract, Du et al., Lysosomal acid lipase deficiency: correction of lipid storage by adenovirus-mediated gene transfer in mice. *Hum Gene Ther.* 13(11): 1361-72, 2002).

With regard to routes of administration, claimed invention encompasses a method for providing any biologically active lipid hydrolytic protein to any cells of any mammal having

deficiency in any biologically active lipid hydrolytic protein, said method comprising any route of administration into cells any vector comprising and expressing any DNA sequence encoding any biologically active lipid hydrolytic protein and expressing the DNA sequence in said cells to produce the said biologically active lipid hydrolytic protein. Practicing the claimed invention as broadly as claimed would require administration by any medically accepted means for introducing the therapeutic directly or indirectly into a tissue *in vitro* or *in vivo*, including but not limited to injections (e.g., intraperitoneal, intravenous, intraarterial, intramuscular, transendocardial, subcutaneous, intracranial or catheter); oral ingestion; intranasal or topical administration; and the like. The choice of a particular route of administration for providing a given a lipid hydrolyzing protein and a particular route of administration suitable for a method comprising providing in a tissue with polynucleotide encoding a lipid hydrolyzing protein may not be applicable to a method comprising providing in other tissue with polynucleotide encoding other lipid hydrolyzing protein.

While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired sites has continued to be unpredictable and inefficient for the past decade. This statement is supported by numerous teachings available in the art. For example, **Pouton et al.** (Pouton and Seymour, Key issues in non-viral gene delivery, *Adv Drug Deliv Rev.* 46(1-3): 187-203, 2001) reviewed the issues in non-viral gene delivery and stated "direct injection of gene medicines into target tissue represents a far simpler task than targeting delivery to a specific tissue from the systemic circulation". See last full sentence on page 188, right column, and section 2.1. Pouton et al. added that there were "no systems yet available for efficient tissue targeting following systemic delivery." (See page 189, first sentence of section 2.2.). **Johnson-**

Saliba et al. stated that although thousands of patients have been involved in clinical trials for gene therapy, using hundreds of different protocols, true success has been limited. A major limitation of gene therapy approaches, especially when non-viral vectors are used, is the poor efficiency of DNA delivery to the nucleus; a crucial step to ensure ultimate expression of the therapeutic gene product (See abstract, Johnson-Saliba et al. Gene therapy: optimizing DNA delivery to the nucleus. *Curr Drug Targets.* 2(4): 371-99, 2001). More recently, **Read et al.** (Read et al., Barriers to gene delivery using synthetic vectors, *Adv Genet.* 53: 19-46, 2005) stated after the time the invention was filed that the "lack of suitable vectors for the delivery of nucleic acids... represents a major hurdle to their continued development and therapeutic application" (see abstract, sentence bridging pages 19 and 20. Problem areas included obtaining persistence in the circulation, gaining access to target cells, and distinguishing target cells from non-target cells. See e.g. page 22). Finally, **Dobson** (Dobson, Gene therapy progress and prospects: magnetic nanoparticle-based gene delivery. *Gene Ther.* 13(4): 283-7, 2006) reviewed the development of non-viral transfection agents for gene delivery stated "While magnetic targeting appears to hold significant potential for gene therapy, there are still major obstacles to employing this technique in the clinic. Perhaps, the problem that is most difficult to overcome is, as with magnetic targeting for drug delivery, that of scale-up." (See Prospects on page 286).

The predictability or lack thereof in the art: As stated in the proceeding section, there is lack of predictability in the art regarding the administration of a vector comprising and expressing a DNA sequence encoding a biologically active lipid hydrolyzing protein in a mammal having deficiency in a biologically active lipid hydrolyzing protein.

It is worth noting that the publication date of Du et al. is July 20, 2002, in which Du H. and Grabowski G --- inventors of instant application --- are the co-authors of the published paper. The Examiner further notes that the priority date of instant application is determined to be 02/02/2001 (See details in the prior art section of this office action).

The amount of direction or guidance: The specification of the provisional application 60/180,362 filed on 02/04/2000 of instant application disclosed administration of enzyme into cells, a protein therapy; however, the application 60/180,362 did not disclose administration of DNA sequences encoding the said enzyme. In this regard, the application 09/775,517 filed 02/02/2001 (now U.S. Patent No: 6,849,257), a parent application of instant application, did disclose vectors expressing proteins.

The presence or absence of working example: The specification of the application 09/775,517 filed 02/02/2001 (now U.S. Patent No: 6,849,257), a parent application of instant application, only contemplates on a method of gene therapy comprising administration of a vector comprising a polynucleotide sequence encoding a lipid hydrolyzing protein to a mammal having a deficiency in the said lipid hydrolyzing protein. No working example was provided in the specification of 09/775,517 filed 02/02/2001 (now U.S. Patent No: 6,849,257).

In addition to the abovementioned issues in administration of a vector comprising a polynucleotide sequence encoding a lipid hydrolyzing protein to a mammal having a deficiency in the said lipid hydrolyzing protein, the phrase "at least 85% sequence homology to lysosomal acid lipase" recited in claim 54 of instant application was not enabled because one skilled person in the art cannot make and use the claimed invention that are not described. As discussed

previously, in the absence of any polypeptide sequences of any lysosomal acid lipase disclosed in the specification, what would be the basis for determination of the phrase "at least 85% sequence homology"? Moreover, based on the information disclosed in the specification of instant application, a lysosomal acid lipase (LAL), a member of the lipase family, is a 372 amino acid glycoprotein (See lines 1-2, paragraph [0037], instant application), 15% of 372 amino acids would account for more than 55 amino acids. Each amino acid could be altered to one of the other 19 amino acid residues (when only L-form standard amino acid residues is considered); accordingly, there would be 19^{55} different variations, which is equivalent to 2.1×10^{70} different patentably distinct polypeptides.

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 51-61.

Priority

5. This application 10/776,797 filed on 02/11/2004 is a DIV of 09/775,517 02/02/2001 PAT 6,849,257 which claims benefit of 60/180,362 filed 02/04/2000. It is noted that the claims of instant application recites administration into cells a vector comprising and expressing a DNA sequence encoding either biologically active lipid hydrolyzing protein or polypeptide (claim 51) or biologically active lysosomal acid lipase (claim 56). *The provisional application 60/180,362 filed on 02/04/2000 disclosed administration of enzyme into cells, a protein therapy; however, the application 60/180,362 did not disclose administration of DNA sequences encoding the said*

enzyme. In this regard, the application 09/775,517 filed 02/02/2001 (now U.S. Patent No: 6,849,257) did disclose vectors expressing proteins. Therefore, the priority of instant application is determined to be 02/02/2001.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 51-54, and 56-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Xiao et al. (Xiao et al., U.S. Patent Application Publication No: 2004/0038365, Publication date Feb. 26, 2004).

It is noted that Xiao disclosed the information encompassed by the claimed invention of the instant application. However, neither Xiao nor instant application provides enabling support for their claimed inventions. Therefore, there is no contradiction between the art rejection stated here and the rejection under 35 U.S.C 112, first paragraph.

Xiao teaches **(i)** regulation of human lysosomal acid lipase (See title, Xiao, 2004), **(ii)** human lysosomal acid lipase can be regulated to treat cancer, CNS disorders, obesity, COPD, diabetes, and cardiovascular disorders (See paragraph [0234], Xiao, 2004), **(iii)** about 80% of

cystic fibrosis patients develop pancreatic lipase deficiency shortly after birth (See paragraph [0007], Xiao, 2004), and there are diseases characterized by a *deficiency in activity of lysosomal acid lipase* that result in massive accumulation of cholesteryl esters and triglycerides in most tissues of the body (See paragraph [0008], Xiao, 2004), **(iv)** a variety of expression vector/host systems can be utilized to contain and express sequences encoding a lysosomal acid lipase polypeptide. These include, but are not limited to, *plasmid, virus expression vectors*, and animal cell expression systems (See paragraph [0131], Xiao, 2004), for example, if an *adenovirus* is used as a expression vector, *sequences encoding lysosomal acid lipase polypeptides* can be ligated into an adenovirus transcription/translation complex comprising the late promoter and tripartite leader sequence (See paragraph [0140], Xiao, 2004), **(v)** suitable *liposomes* for use in the present invention include those liposomes standardly used in, for example, *gene delivery methods* known to those of skill in the art (See paragraph [0261], Xiao, 2004), and **(vi)** pharmaceutical compositions of the invention can be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, parenteral, topical, sublingual, or rectal means (See paragraph [0226], Xiao, 2004).

With regard to the limitation at least 85% sequence homology to lysosomal acid lipase (claim 54 of instant application), it is noted that the limitation reads on either 85% homology for the entire polypeptide sequences or 85% homology within a subset of the polypeptide sequences of various length. In this regard, Xiao teaches that human lysosomal acid lipase polypeptide variants, which are biologically active, e.g., retain a lipase activity, also are lysosomal acid lipase polypeptides. Preferably, naturally or non-naturally occurring lysosomal acid lipase

polypeptide variants have amino acid sequences which are at least about 54, 60, 65, or 70, preferably about 75, 80, 85, 90, 96, 96, or 98% identical to the amino acid sequence shown in SEQ ID NO: 2 or a fragment thereof (See paragraph [0090], Xiao, 2004).

It is noted that *lysosomal acid lipase* recited in claim 56 is a *lipid hydrolyzing protein* recited in claim 51.

Thus, Xiao clearly anticipates claims 51-54, and 56-61 of instant invention.

7. Claims 51-54 and 56-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Kapeller-Libermann (Kapeller-Libermann, U.S. Patent Publication No: 2002/0193303, Publication date, Dec 19, 2002)

It is noted that Kapeller-Libermann disclosed the information encompassed by the claimed invention of the instant application. However, neither Kapeller-Libermann nor instant application provides enabling support for their claimed inventions. Therefore, there is no contradiction between the art rejection stated here and the rejection under 35 U.S.C 112, first paragraph.

Kapeller-Libermann teaches **(i)** 58860, a human cholesteryl ester hydrolase and uses therefor (See title, Kapeller-Libermann, 2002), and recombinant expression vectors containing 58860 nucleic acid molecules, host cells into which the *expression vectors* have been introduced, and therapeutic methods utilizing compositions of the invention (See abstract, Kapeller-Libermann, 2002), **(ii)** the "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked and can include a *plasmid*, cosmid

or viral vector. The vector can be capable of autonomous replication or it can integrate into a host DNA. *Viral vectors* include, e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses (See paragraph [0167], Kapeller-Libermann, 2002), **(iii)** identification of a protein sequence domain between ***lysosomal acid lipase*** and *cholesteryl ester hydrolase*, and the domain corresponds to amino acid sequences of human 58860 at 94 to 221 of SEQ ID No: 2 disclosed by Kapeller-Libermann (See paragraphs [0036], Kapeller-Libermann, 2002), **(iv)** cholesteryl ester hydrolase-associated disorder includes a disorder, disease or condition which is characterized by *a misregulation of a cholesteryl ester hydrolase mediated-activity or by an abnormal cholesteryl ester hydrolase-mediated activity* (See lines 1-5, paragraph [0051], Kapeller-Libermann, 2002), and there are many cholesteryl ester hydrolase-associated disorders (See paragraphs [0055]-[0058], Kapeller-Libermann, 2002), **(v)** both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant or unwanted 58860 expression or activity (See paragraphs [0318], Kapeller-Libermann, 2002), **(vi)** the *nucleic acid* and polypeptides, fragments thereof, can be incorporated into pharmaceutical compositions (See paragraphs [0296], Kapeller-Libermann, 2002), a pharmaceutical composition is formulated to be compatible with its intended route of *administration*; and examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration (See paragraphs [0297], Kapeller-Libermann, 2002), and *liposomal suspensions including liposome* can be used for administration (See paragraphs [0304], Kapeller-Libermann, 2002).

With regard to the limitation at least 85% sequence homology to lysosomal acid lipase (claim 54 of instant application), it is noted that the limitation reads on either 85% homology for the entire polypeptide sequences or 85% homology within a subset of the polypeptide sequences of various length, including the domain shared by *lysosomal acid lipase* and *cholesteryl ester hydrolase* (See paragraphs [0036], Kapeller-Libermann, 2002). In this regard, Kapeller-Libermann teaches a preferred embodiment also has one or more of the following characteristics: it has a molecular weight, amino acid composition or other physical characteristic of a 58860 protein of SEQ ID NO: 2; or it has a lipase serine active site signature sequence which is preferably about 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% or more, identical with amino acid residues 167-176 of SEQ ID NO: 2;(See paragraphs [0123, and [0126] Kapeller-Libermann, 2002).

Thus, Kapeller-Libermann clearly anticipates claims 51-54, and 56-61 of instant invention.

Conclusion

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-

3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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